Detection of Environmental Cancer Hazards: Epidemiologic Methods*

ROBERT N. HOOVER, M.D., Bethesda, Maryland

The majority of human cancers are environmentally caused and hence are preventable. The epidemiologic method is a major technique to identify causative agents. The clinician can uncover clues to etiology by careful observation of patients and can assist by cooperating with the investigative epidemiologist.

It is widely accepted that the majority of human cancers are environmentally caused and hence preventable. It is important to keep in mind the definition of environment. Here environment means anything other than a person's genetic makeup. This includes exposure to occupational factors, toxic chemicals in the general environment, natural and artificial constituents of the diet, drugs, and cigarette smoking, and to other exposures related to personal habits. The environmental origin of most human cancer is apparent from studies of geographic variations in cancer incidence and mortality among genetically similar populations, and the almost universally observed movement of cancer incidence rates in migrant populations away from the rate prevailing in their homeland and toward the rates prevailing in their adopted homelands. It has been fashionable among some to attempt to quote a percentage of human malignancy that can be attributed to environmental exposures. Based on our current level of understanding of the carcinogenic process, this is a naive and misleading exercise. Like most other diseases, cancer is due to a complex interaction of many causal factors. Based on what we now know, it is reasonable to contend that nearly all human cancers are environmentally induced and, at the same time, that close to 100 percent of human cancers are influenced by host factors. In other words, almost all of human cancer requires exposure to a carcinogenic agent by an individual who is susceptible to the carcinogenic action of that agent. Supporting this opinion are the observations that it is extremely rare for a genetic condition to result in a 100 percent attack rate of cancer, and equally as rare for an environmental exposure to cause a 100 percent attack rate in all those exposed. This is not a new concept for the same holds true for every infectious disease. A person does not develop clinical tuberculosis without exposure to the tubercle bacillus. Just as certainly, this person does not become a clinical case of tuberculosis without possessing the complex web of nutritional, immunologic, and other host factors which made him susceptible to the action of the bacillus.

If all this is so, then there are two potential avenues for preventing human cancer, just as there are the same two avenues for preventing infectious diseases. One is to manipulate the environment in order to prevent exposure to carcinogenic agents and the other is to manipulate the host's susceptibility to the carcinogenic potential of environmental agents. Currently, we do not prevent cholera in this country by immunization but by keeping people from drinking sewage. On the other hand, we do little to prevent environmental exposure to the polio virus, but attempt to alter our children's susceptibility to this agent. While manipulation of

*Presented at the Fourth Annual Governor's Conference of the Medical Society of New Jersey, May 6, 1978, Atlantic City. Dr. Hoover is Head of the Environmental Epidemiology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland. He may be addressed there—Room C307, Landow Building.

host susceptibility eventually may be realized for cancer, there is no evidence that such possibilities exist in the near future. On the other hand, there is a growing body of evidence that interruption of exposure to carcinogenic agents can result in cancer prevention *now*. Therefore, it seems appropriate to place a heavy emphasis on the identification and removal of carcinogens in our environment.

One major mode of identifying disease-causing agents is the *epidemiologic method*. As you may recall from your sophomore medical student days, epidemiology is the study of the distribution and determinants of disease frequency in humans. In general, epidemiology affords two methods to evaluate the influence of environmental exposures on the development of cancers. One method is *descriptive epidemiology*, which attempts to evaluate the risk of various diseases in large population groups about which something is also known with respect to potential causes of these diseases. These population groups can be defined in a number of ways, e.g., by place of residence, year, race, age, and so on. The other method available is *analytic epidemiology*. In these studies attempts are made to obtain information on the possible causes of disease in specific individuals. By aggregating large numbers of individuals on which this information has been collected, a more precise determination of causal factors can be made than can be done by the more descriptive approaches.

Rather than go into a didactic discussion of epidemiologic methods which will just as certainly put you to sleep now as it did when you were in medical school, I will illustrate these two major methods in epidemiology (descriptive and analytic studies) by referring to specific examples in which I have been involved in the past several years.

DESCRIPTIVE EPIDEMIOLOGY

As mentioned, descriptive epidemiology relies on information from large population groups identified by place of residence, year, race, age, or other variables. Specific examples involving variation by time, geography, and race point out some of the values of these methods as well as some of the pitfalls.

With respect to time trends, persons who de-emphasize the impact of chemical exposures on human cancer—either in the occupational or general environmental setting—often point out that since the rapid expansion in the manufacturing and use of man-made chemicals in this country, the overall incidence of cancer has risen only slightly in males and actually has declined in females. However, it seems unwise to use these observations to discount the influence of man-made chemicals. It is wrong to suggest that all cancer combined (or even all cancer minus lung cancer) is a meaningful measure of disease as far as etiologic research is concerned. It is wrong to imply that somehow we know the base-line level of cancer risk in the absence of all newly produced chemicals. And finally it is wrong to imply that the effects of newly produced chemicals could be gauged through current rates for cancer. The slight decline in cancer rates once lung cancer is excluded is due largely to the sharp decrease in the incidence of stomach cancer in both sexes, and invasive cancer of the uterine cervix in females. There is currently no reason to believe that either of these impressive declines is due to the proliferation of man-made chemicals in our environment. Cancer (even cancer excluding lung cancer) is certainly not one disease. Grouping diseases which have different causes greatly impairs our ability to identify the origins of specific illnesses. For example, while the total cancer incidence rates (minus lung) declined slightly between the late 40's and the early 70's, the following trends have been observed for specific sites of cancer. Cancer of the esophagus has risen by 117 percent in nonwhite males and 127 percent in nonwhite females. Cancer of the intestines has risen by 19 percent in white males and 68 percent in nonwhite males. Cancer of pancreas has increased by 16 percent in white females, 20 percent in white males, 42 percent in nonwhite males, and 100 percent in nonwhite females. Malignant melanoma of the skin has increased by 85 percent in white males and 42 percent in white females. Prostatic cancer has increased by 21 percent in white males and 57 percent in nonwhite males. Bladder cancer has increased by 24 percent in white males and 104 percent in nonwhite males. Cancers of the kidney, renal pelvis, and ureter have increased by 58 percent in white males and 44 percent in nonwhite males. Cancer of the thyroid gland has increased by 50 percent in white females and 100 percent in white males. The incidence of lymphoma has increased by 39 percent in white males, 49 percent in white females, 74 percent in nonwhite females and 82 percent in nonwhite males. Other trends might be cited, but I think this should be sufficient to illustrate the profound increases in the risk of certain cancers just in the period from 1947 to 1970. We hope these epidemiologic observations will point to hypotheses that we can test in more analytic studies.

One should not take much solace in the lack of increase for other specific sites. Since we are largely ignorant of the causes of most cancer, we really do not know what to expect the trend of cancer to be in the absence of the recent chemical revolution. For example, the stable incidence rates for endometrial cancer between 1947 and 1970 were interpreted as exonerating a newly introduced carcinogen. That evaluation was subsequently shown to be profoundly wrong, since cancer of the endometrium now clearly has been linked with the use of a particular pharmacologic agent—estrogens for the treatment of the menopause. The unchanging time trend prior to the 1970's masked this problem for several reasons, particularly the rising rate of elective hysterectomy over the past 30 years, which effectively reduced the total number of women at risk of developing this tumor. Lastly, the interval between the time that a hazardous exposure occurs and the time that it is manifest by the diagnosis of a tumor is usually quite long. For some very potent occupational bladder cancer carcinogens this average latent period was about 18 years and, for some less potent occupational carcinogens, it has been estimated to be in excess of 40 years.

Another descriptive method for evaluating the influence of various factors on the risk of cancer is geographical variation in the frequency of cancer. Several years ago we published a very large book of numbers. This book contained the age-adjusted rate for each of four race-sex groups for 35 different sites of cancer in each of the 3,056 individual counties of the United States. We felt that this publication might be a major research resource for identifying cancer patterns that might lead to identification of specific causes, but it hit the research community with a resounding thud. While we began to work with the material, very few other people did. We then tried to turn some people on to these data by illustrating them in the form of maps and we produced two atlases of cancer mortality by county in the United States. The rest is history, well known to all of you. These illustrations of the nonrandom distribution of cancer risk in this country have had an enormous effect on the research community, governmental agencies, and even the general public. Some of the sequela may have been due to inappropriate interpretations of these

maps. However, for the most part, the reactions and interests generated by these maps have been one of the healthiest spurs to disease prevention that have occurred in some time in this country.

Figure 1 illustrates the distribution of cancer mortality rates in white males for all sites of cancer combined. As you will note, New Jersey is well represented with a number of counties with rates in the top 10 percent of all counties in the country. The general pattern of distribution of counties with high rates that is illustrated—concentrated in the northeast, urban centers in the midwest, and in some southeastern and southern coastal areas—reflects primarily the distributions for two of the more common sites in males, i.e., lung cancer and colon cancer. High rates in the northeast and urban midwest also characterize the situation for females with respect to colon cancer and breast cancer. However, each specific site of malignancy has its own characteristic distribution.

Figure 2 illustrates the distribution of cancer death rates for malignant melanoma of the skin. High rates predominate in the south, and low rates in the north. In fact, there is almost a linear relationship between the magnitude of the rate and the latitude in which the county is situated, illustrating the underlying association of this tumor with exposure to ultraviolet irradiation in the form of sunlight. Figure 3 illustrates the distribution of mortality rates for stomach cancer among white males. The two major high-risk areas are in the northern portion of the north central region of the United States and in the southwestern states. These areas correspond with those areas where migrants from countries experiencing very high stomach cancer rates have settled (Scandinavia, Germany, Austria, and Mexico). Figure 4 illustrates the mortality rates among white males for cancers of the urinary bladder. As you will note, New Jersey stands out particularly prominently in this map. Nineteen of the twenty-one counties in the state of New Jersey have rates for bladder cancer which place them in the top 10 percent of all counties in the United States. As you are well aware, the state of New Jersey is also the state with the highest concentration of the chemical industry. In fact, correlating industrial patterns on the national level with the rates of bladder cancer reveals a strong and consistent relationship with the presence of the organic chemical industry. Since bladder cancer is the tumor most closely linked to occupational exposures and many of these are in the chemical industry, New Jersey's high rates may be explicable on this basis.

ANALYTIC EPIDEMIOLOGY

While descriptive epidemiology can give us clues to potential causes of disease, it remains for the much more refined techniques of analytic epidemiology to provide pursuasive evidence of causality. While epidemiology in general, and analytic studies in particular are enjoying renewed emphasis, the number of epidemiologists and good analytic studies in the area of environmental cancer still remain quite small. Therefore, we can consider the whole area of environmentally induced malignancy as almost unexplored territory, as only a few of the hypotheses raised in descriptive studies yet have been evaluated. Two recent studies in which our branch has been involved, however, illustrate the need for this type of study. The first field study that was initiated in response to the geographic distribution by county was a study designed to investigate the abnormally high rates of lung cancer in the predominantly rural areas of the coastal southeastern United States. An intensive interview study of lung cancer patients and the comparison individuals from this region has revealed that a portion of the excess appears to be attributable to only very brief exposures that these individuals had working in shipyards during World War II. Of particular interest is the observation that the excess appears to apply to a number of different jobs within the shipbuilding industry, not simply those that involved the application of asbestos. Another analytic epidemiologic study which currently is being conducted involves New Jersey in a major way. This study is a case-control interview study of all newly diagnosed bladder cancer cases in ten separate areas of the United States—including the entire State of New Jersey. The interview involves obtaining information on the use of tobacco products, life-time occupational histories, life-time residence histories, exposures to artificial sweeteners, and a number of other potentially hazardous exposures. It is our hope that this study will reveal specific, potentially preventable, exposures which may be responsible for a portion of the bladder cancer excess as seen in the State of New Jersey and elsewhere.

In evaluating the various methods that epidemiology has to identify environmental hazards, it is important to recognize both the strengths and the weaknesses of the epidemiologic approach.

STRENGTHS AND WEAKNESSES OF EPIDEMIOLOGY

The strengths of the epidemiologic method are two-fold. First of all, this method allows the direct measurement of the risk of cancer due to an exposure in a *human* population. It thus can identify causes of cancer in *humans* that are associated with intermediate or high levels of risk. Secondly, there is a much less obvious role and strength of the epidemiologic method. That is, these kinds of studies can allow someone to gain insights into the basic mechanisms of a disease causation (for cancer, the mechanism of carcinogenesis).

If these are the strengths of epidemiology, then what are its weaknesses? There are at least five major weaknesses to the epidemiologic approach. First of all, as you may have inferred from my emphasizing that epidemiology was reasonably strong in identifying intermediate and high levels of risk, it is quite weak at identifying the causes of very *low* levels of risk. Very small differences in risk between a group exposed to some substance *versus* that in a group not exposed to it could be due to a variety of reasons. For example, chance or other differences between the exposed and unexposed which we either do not know about or which we cannot control adequately. Because of this, it becomes next to impossible to say with any assurity that a very low level of risk is caused by a similarly low-level exposure to some substance. What do we mean by low level of risk? The lowest excess cancer risk that is directly observable in a group of exposed individuals and is generally accepted as being due to that exposure and not some other factor is the 30 percent excess risk of childhood leukemia among children who were exposed to radiation *in utero* in the last trimester of pregnancy (pelvimetry). Indeed, it has taken us some 20 years to become reasonably convinced of this 30 percent excess risk.

The second weakness of the method, and perhaps its most important weakness, is what is referred to as latent period or induction—incubation period. This is the interval between exposure to a cause of a disease and the actual manifestation of the disease itself. For cancer-causing exposures these latent periods are quite long—from five years to over 50 years.

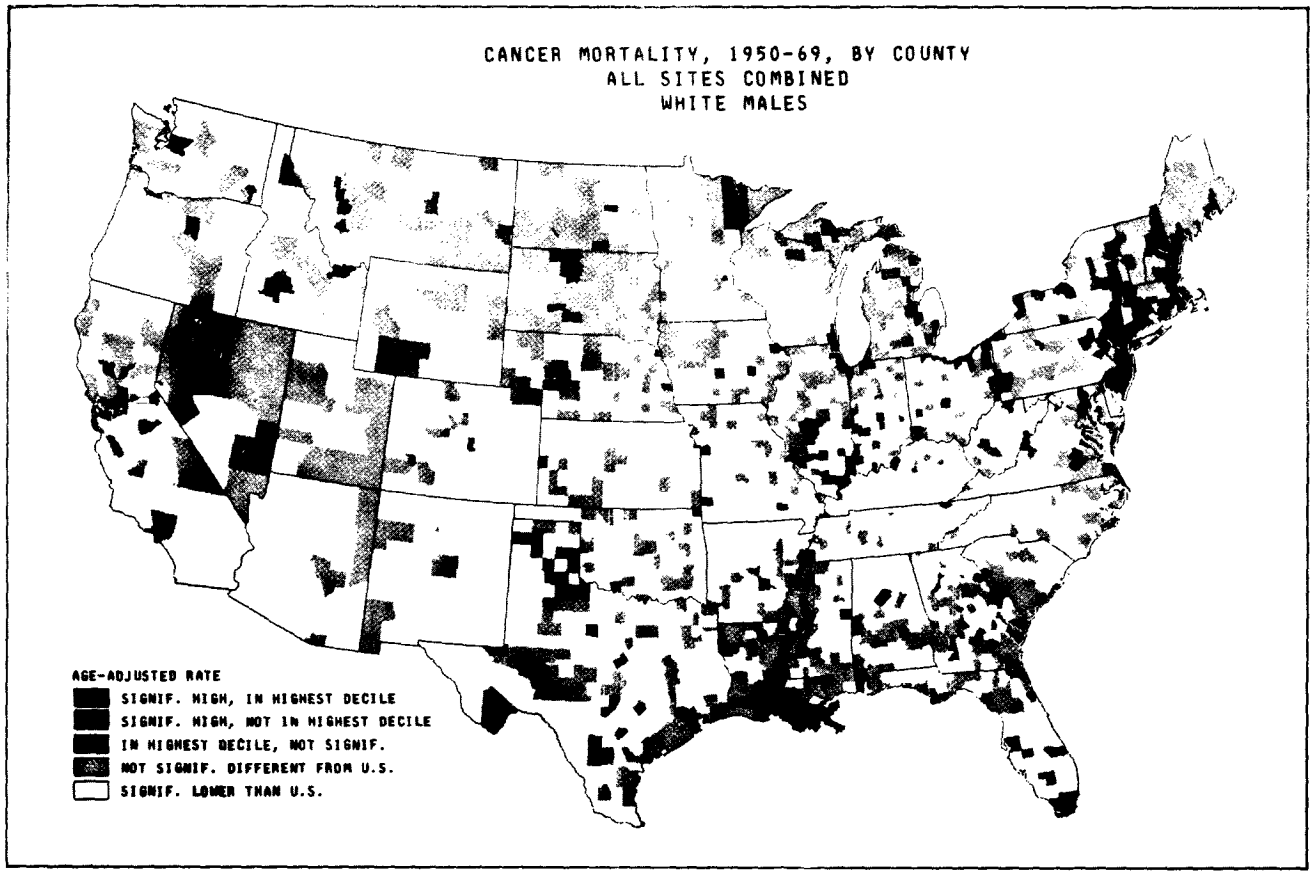

Figure 1

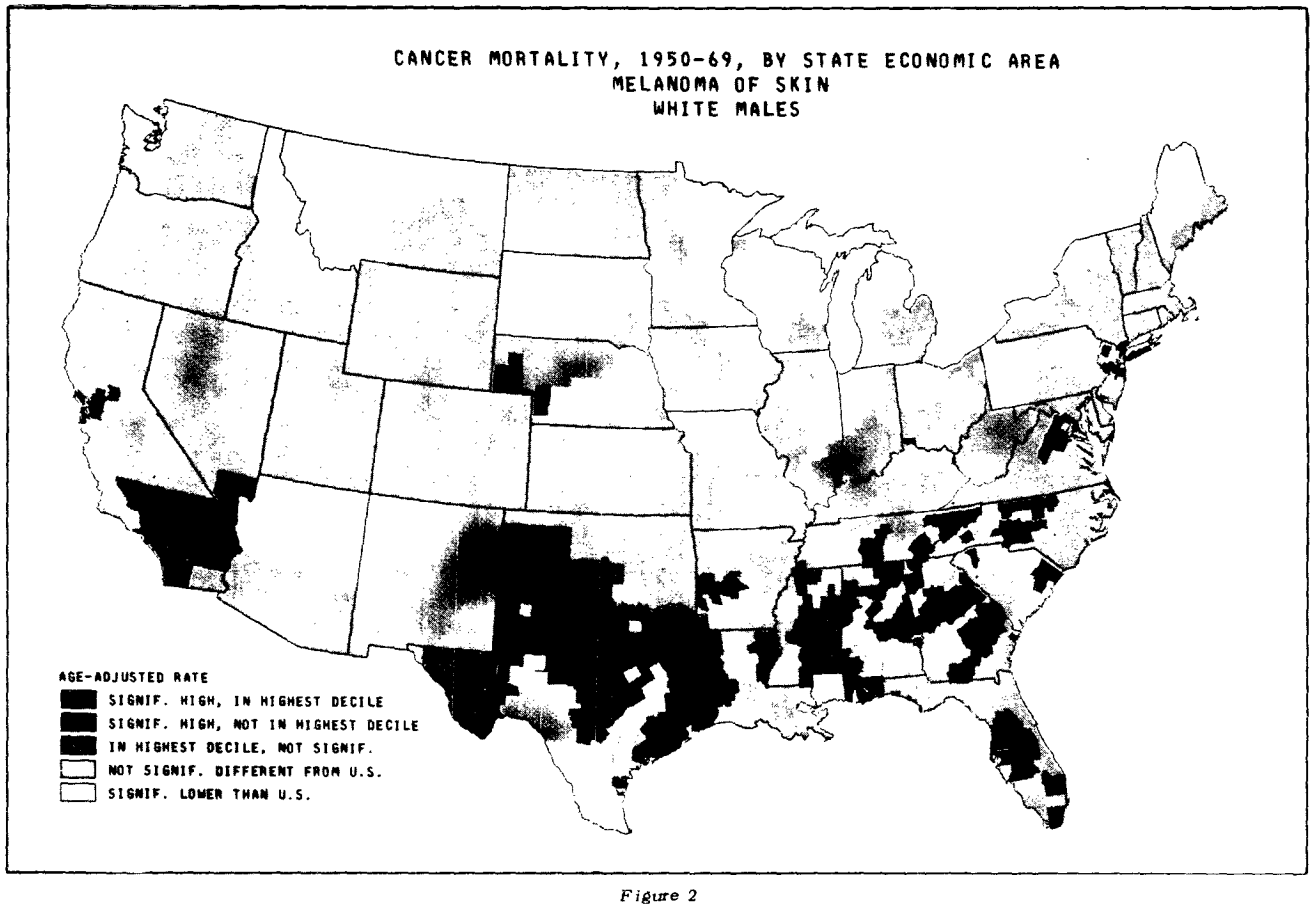

Figure 2

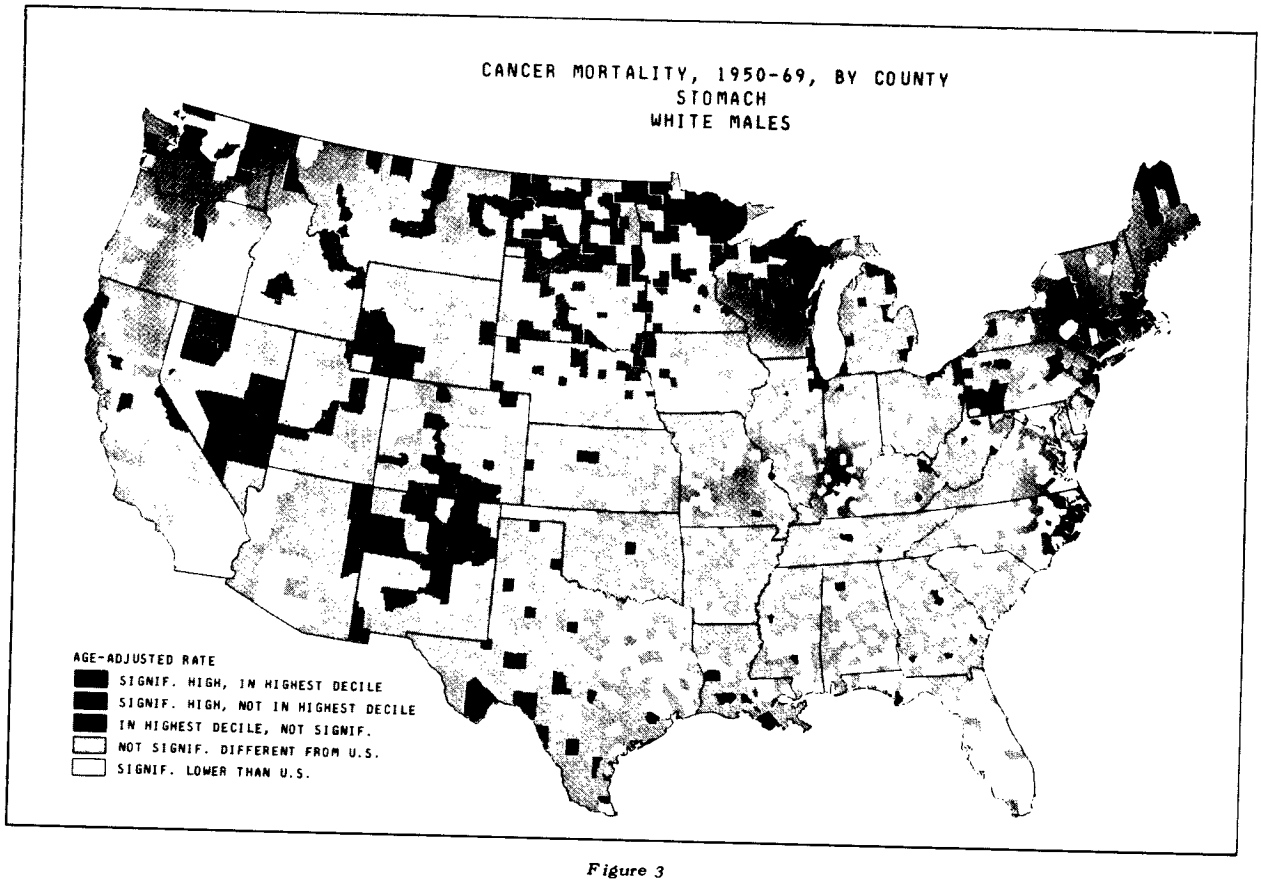

Figure 3

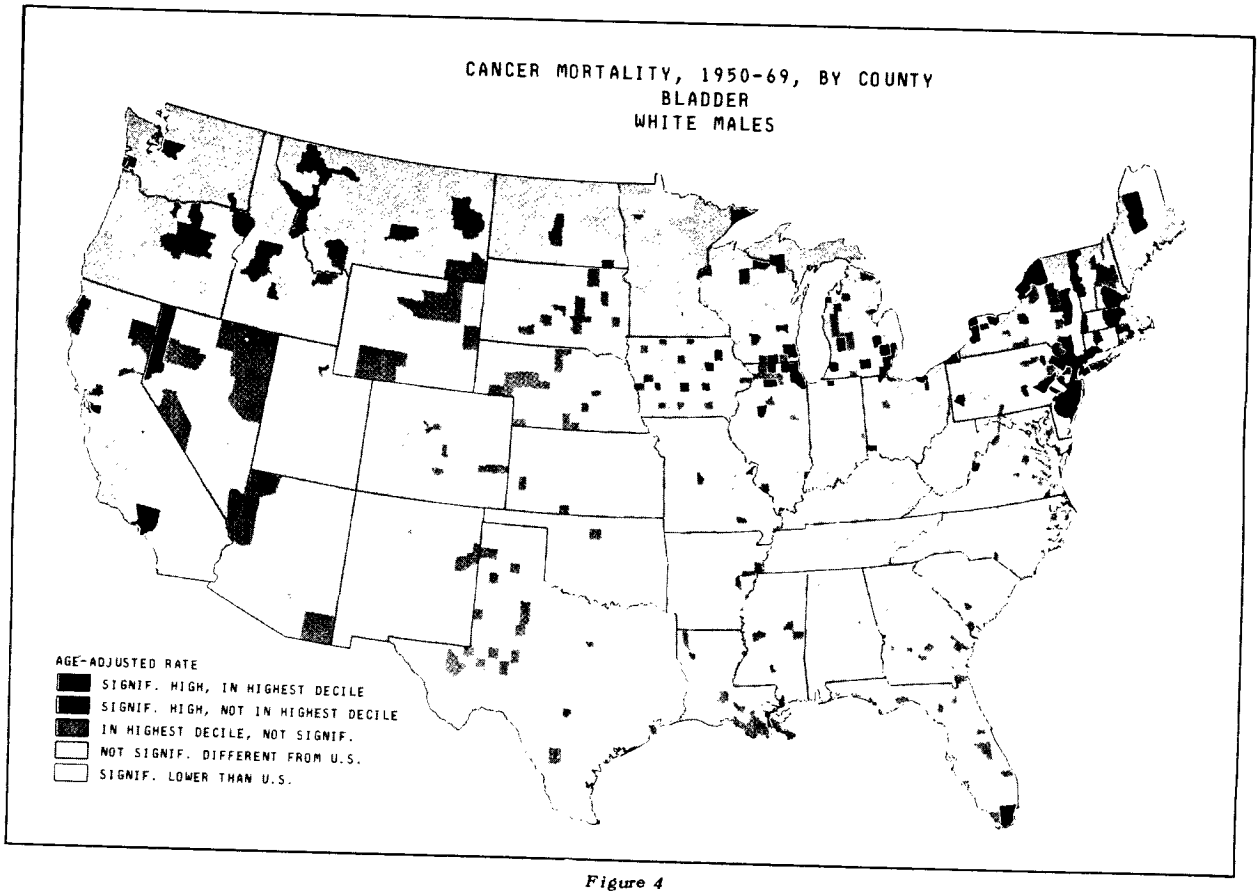

Figure 4

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The third weakness of the method is the lack of specificity of exposure. Usually epidemiologists study the effect of exposure to mixtures of chemicals or other agents rather than pure exposures to a single toxic substance.

The fourth weakness is the inability to control the unknown risk factors for the disease in question. In an experiment we hope that the randomization procedure introduces some control for unknown factors. In observational studies, we can control for known confounding factors, but obviously cannot guarantee control for unknown confounders.

The last weakness of the approach encompasses the practical problems involved in epidemiology. In order to function effectively an epidemiologist needs to have access to appropriate information on large groups of people. Sometimes this is possible, but sometimes the information just does not exist. Furthermore, there currently is a lack of enough competent epidemiologists even to evaluate adequately the information that does exist.

ROLE OF CLINICIAN

What does all of this mean for the practicing physician in the State of New Jersey? As illustrated, New Jersey has been prominent in some of our undertakings. It reflects the same trends that we see in a number of urbanized, industrialized areas in this country for a number of cancer sites; in addition, for some cancers New Jersey actually seems to be particularly exemplary of some problems. But what does it mean for the practicing physician? Here is where I have an opportunity to do a little proselytizing. While all of you cannot participate in the laboratory animal approach to identification of cancer hazards, all of you can participate in the epidemiologic approach. If there is one thing that we have learned in the course of identifying causes of cancer and birth defects in humans, it is that the most productive source of clues for these agents is the alert clinician. Every clinician should be an etiologist in his own right. The observation of the relationship between aromatic amines and bladder cancer was originally that of a German surgeon, who noticed an abnormal frequency of bladder cancer occurring in the workers in one specific plant. You may be aware of the vinylchloride story, which was the result of an alert observation by an industrial physician working for the B.F. Goodrich Company. The identification of diethylstilbestrol as a transplacental carcinogen was the result of an astute observation by an inquisitive gynecologist at the Massachusetts General Hospital. There are many other examples, but the point is clear. The practicing physician should keep etiology as well as therapy in mind. He should be attuned to the kinds of patients he sees, their occupations, their personal habits, their dietary habits, the drugs they take, and so on. An alert and inquisitive clinician can be one of the most productive epidemiologists.

The second way in which clinicians can be involved in identifying environmental causes of disease is by active cooperation with investigators who are pursuing some of the more systematic approaches. I mentioned that part of our systematic evaluation of geographic patterns of cancer in this country involves getting into specific analytical studies in selected high-risk areas in order to follow up on the clues that have been generated. One of our first attempts in this direction is the investigation of bladder cancer in the State of New Jersey, in collaboration with your State Health Department. The response of the medical community of this State has been remarkably gratifying. You all have shown more interest and concern than we had hoped. Pathologists have opened their log books to identify cases. The urologists and family practictioners have granted permission to approach their patients for interviews. I thank you for that cooperation and encourage you to persist in it.

CONCLUSION

Those of us who pursue systematic approaches are totally dependent on the good will and cooperation of those physicians who actually see the patients and make the diagnoses. We only can function and only can identify preventable causes of disease with your cooperation. Without it we cannot do anything. I hope you will continue to support these efforts, as I think it is in the true spirit of concern for patients, as well as for society, which is a feature of physicians in general and this State Medical Society in particular.